

REMARKS

Claims 19-20, 22-27, 29-35, and 54-67 were pending in the subject application. By this amendment, claims 20, 34 and 54-67 are cancelled and new claims 68-69 are added. Claims 19-20, 22-27, 29-35, and 54-67 were rejected as obvious under 35 U.S.C. § 103 over United States Patent No. 6,034,267 (“Gierskcky”). The Examiner states that Gierskcky teaches, *inter alia*, ALA-ester compositions for treating or diagnosing and that such compositions generally contain ALA-esters at a concentration of 1-50% and can contain a chelating agent. The Examiner also states that Gierskcky does not specifically disclose the use of ALA-ester concentrations below 1% or the use of the instant pH ranges. *See* Office Action at 3 (February 21, 2007).

Claims 19, 22, 29, 32, 33, and 35 have been amended by deleting the term “an ester of 5-aminolevulinic acid (E-ALA)” and replacing it with the term “ALA hexylester (h-ALA).”

In view of the fact that, if the pending composition claims are allowed, then withdrawn method of use claims may be rejoined if they depend from or otherwise require all the limitations of an allowable claim, *see* MPEP 821.04, the Applicants hereby also amend withdrawn claims 36 and 45 to recite “the pharmaceutical preparation of claim 19” and amend withdrawn claims 36, 37, and 46 by deleting the term “an ester of 5-aminolevulinic acid (E-ALA)” and replacing it with the term “ALA hexylester (h-ALA).” Withdrawn claims 51 and 52 are also amended to correct claim dependency.

Applicants submit that the present amendment adds no new matter. Support for the amendments is found at, *inter alia*, paragraphs 0008-0009, 0011, 0018-0022, 0025-0031, 0034-0035 of the published application.

Upon entry of the present amendment, Claims 19, 22-27, 29-33, and 35 will be pending and under examination. Applicants respectfully request entry of this amendment.

Claim Rejections under 35 U.S.C. § 103

Rejection of claims 20, 34, and 54-67 is rendered moot by the cancellation of these claims. The remaining rejections are addressed below.

This amendment follows a telephone interview on April 10th, 2007 with the Examiner and Supervisory Examiner in this case. During the interview, the present amendments and elaboration on the previously presented data relating to unexpected results were discussed. In light of that interview, Applicants here focus their remarks on clarifying the data previously submitted in support of Applicants’ claim of unexpected results for various ALA esters, particularly ALA hexylester (h-ALA).

During the interview, clarification of two sets of data was discussed. One of these, Exhibit E of the Petition Under § 1.181, submitted on March 19, 2004, presents in graph form the "Dose-Response of Different ALA-esters on the Pig Bladder Model." The exhibit referred to as "E" by the applicants in the Rule 181 Petition was later hand-marked "Exh. g" by the Patent Office. In the interview, the Examiners referred to this as "Exhibit G" while the Applicants referred to the same exhibit as "Exhibit E." The Examiners requested a clearer presentation of the data and clarification regarding the ALA ester concentrations represented in the original graph.

Applicants refer the Examiners to Exhibit A of this Amendment (references to Exhibits attached to this amendment are underlined for the sake of clarity; references to Exhibits of papers previously filed are not underlined). Exhibit A shows the same data as Exhibit E of the Petition under § 1.181 except that it has been modified such that concentration, measured on the horizontal axis, is expressed in weight/weight % units instead of in molarity units as in the original (published as Marti et al., 162 J. Urology 546 (1999)). The chart is also modified in that it does not include the caption "2 h of incubation" and does not label the highest-concentration data point for ALA octylester "precipitation."

Exhibit A clearly shows that ALA hexylester produces fluorescence at concentrations below 1%. Exhibit B of this Amendment shows a black-and-white copy of the original color chart. As stated in a Table in the same petition (Applicant's Exhibit F to the petition, handmarked by the Patent Office "Exh. H"), ALA hexylester hydrochloride has a molecular weight of 251.8 and thus the maximum fluorescence concentration for ALA hexylester hydrochloride of 4 mM corresponds to a concentration of 1 mg/ml or 0.1% w/w. The Table is attached to this Amendment as Exhibit C.

The Examiners also asked for clarification of an Exhibit of graphs plotting fluorescence vs concentration taken from Uehlinger et al., 54 J. Photochem. Photobiol. B: Biol. 72, 76 (2000). Applicants in the Rule 181 Petition referred to this as "Exhibit C"; it is handmarked in the Patent and Trademark Office copy of the Petition as "Exhibit E." A black-and-white copy of the color original is attached to this Amendment as Exhibit D. A modified version of the same chart is attached to this Amendment as Exhibit E (also submitted in Applicants' Amendment dated June 27, 2005).

According to Uehlinger et al. (attached to this Amendment as Exhibit F), the fluorescence was measured after three hours incubation with the test substances (ALA and ALA esters). See Uehlinger at 76, caption to Figure 3. Figure 3 of Uehlinger shows results for four different human cell lines. Exhibits D and E show results for two of those cell lines, J82 and T24. In cell lines J82 and T24, peak fluorescence was obtained at an ALA hexylester

concentration of about 0.3 and 0.2 mM, or about 0.0075 and 0.005%, respectively. In the other two cell lines, maximum fluorescence for ALA hexylester was similarly observed at a concentration well below 1%: in A549 cells, peak fluorescence was observed at about 1.05 mM ALA hexylester, or about 0.025%, and in BEAS-2B cells, peak fluorescence was observed at about 0.8 mM ALA hexylester, or about 0.02%.

The above explanation addresses the questions raised by the Examiners during the interview. In sum, the data previously submitted shows that, under the various conditions evaluated, at various times of incubation and in different models, ALA hexylester yields peak PpIX fluorescence at concentrations below 1%.

Indeed, the Examiner has acknowledged that the results show that ALA-hexylester yields fluorescence at concentrations below 1%. *See Office Action at 7 (February 21, 2007).*

Further, for the reasons set forth in the Amendment filed December 27, 2006, such results for ALA hexylester are unexpected and therefore are sufficient to overcome the asserted *prima facie* obviousness case on the basis of which the claims were rejected.

Withdrawn Claims Amended for Possible Rejoinder

Claims 36-53 were withdrawn as drawn to non-elected subject matter. The withdrawn claims recite a method of diagnosis (claim 36 and its dependent claims) and a method of treatment (claim 45 and its dependent claims). The withdrawn claims have been amended to recite all the limitations of the independent product claim 19. Applicants note that withdrawn method claims 37, 38, 46, and 47 are rendered moot by the instant amendments.

Where claims to a recited product are found allowable, previously withdrawn method claims directed to a method of using a recited product can be rejoined if they depend from or otherwise require all the limitations of an allowable product claim. *See MPEP § 821.04(b).* In such circumstances, the claims to be rejoined must be considered for patentability. *See id.* Where the amendment is made after final rejection, as here, the amendment could be denied entry if the rejoined process claims raise new issues requiring further consideration. *See id.* In such circumstances, the MPEP recommends that, prior to mailing an advisory action, the applicant be called and given an opportunity to cancel the process claims to put the application in condition for allowance, or to file an RCE. *See id.*

If the product claims as amended herein are found to be allowable, and the amended process claims are rejoined and found to raise new issues requiring further consideration,

Applicants respectfully request that they be given the opportunity to cancel the process claims or file an RCE prior to the mailing of an advisory action.

Cancelled Subject Matter

This Amendment cancels subject matter without prejudice and solely for the sake of expediency with respect to the pending claims. Applicants reserve the right to pursue the cancelled subject matter in a continuation of this Application.

Amendment After Final Action

It is believed that good and sufficient reasons exist as to why the amendments herein are necessary and were not presented earlier. These amendments serve to put the claims into condition for allowance by taking into account the views expressed by the Examiners in an interview after final and incorporating into the independent claims and new dependent claims certain limitations previously presented in the dependent claims. These amendments were not made earlier because it is the applicants' view that the subject matter of the claims removed by this amendment is in fact allowable as novel and non-obvious over the prior art. Nevertheless, that subject matter has been cancelled for the sake of expediency in prosecuting the remaining subject matter to allowance. Applicants submit that this Amendment satisfies 37 C.F.R. § 1.116 and therefore should be entered.

CONCLUSION

All objections and rejections having been addressed, it is respectfully submitted that the present application is now in condition for allowance, which action is respectfully requested. The Examiner is invited to contact Applicants' representative to discuss any issue that would expedite allowance of the subject application.

Respectfully submitted,

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